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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/673,785	12/29/00	NELSON J	41934/23838

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EXAMINER	
KAM,C	
ART UNIT	**PAPER NUMBER**
1653	15

DATE MAILED: 11/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application N .	Applicant(s)	
	09/673,785	NELSON ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this c mmunicati n appears n the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3 is/are rejected.

7)☒ Claim(s) 4-8 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Sequence Amendment

Applicants' sequence amendment and CRF filed on October 9, 2001 (Paper No. 13) has been entered. An amino acid sequence Acety-C-[S-Acm]-VIGYSGDR-C-[S-Acm]-K-[N^{ε}-biotin]-amide is cited at page 18, lines 15-16 in the specification, but no "SEQ ID NO:" is given. Applicants must comply with the requirements of the sequence rules (37 CER 1.81-1.825) and provide a new copy of sequence listing and CRF containing this sequence.

Informalities

The disclosure is objected to because of the following informalities:

1. Amino acid sequences are cited in the specification, but no "SEQ ID NO:" is given (e.g., page 2, line 14). Each amino acid sequence must be identified by a "SEQ ID NO:". Appropriate correction is required.

2. Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. In the specification, applicant has cited Acety-C-[S-Acm]-VIGYSGDR-C-[S-Acm]-K-[N^{ε}-biotin]-amide at page 18, lines 15-16 in the specification in such a manner that appears that the instant brackets would indicate deleted material and is thus, confusing as to whether the peptide would include the sequence "S-Acm" or not. See changes to 37 CFR 1.121 in Amendment rules package (Final Rule published on 8 Sep. 2000 (65 Fed. Reg. 54603), see also O. G. of 19 Sep. 2000 (1238 Off. Gaz. Pat. Office 77)).

Claim Objections

3. Claims 4-8 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 4-8 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide obtained from amino acid residues 33-42 of murine epidermal growth factor ($mEGF_{(33-42)}$) wherein the peptide is modified to protect it from proteolytic degradation, binds to laminin receptors and has substitution of Tyr by Tic-OH or of Arg by citrulline, does not reasonably provide enablement for a peptide derived from $mEGF_{(33-42)}$ wherein the peptide is modified to protect it from proteolytic degradation, binds to laminin receptors and has substitution of Tyr by any Tyr analog or substitution of Arg by any Arg analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-3 encompass a peptide derived from $mEGF_{(33-42)}$ wherein the peptide is modified to protect it from proteolytic degradation, binds to laminin receptors and has substitution of Tyr by a Tyr analog or substitution of Arg by an Arg analog. The specification, however, only discloses cursory conclusions (pages 2-5), which state that a peptide derived from

$mEGF_{(33-42)}$ wherein the modified peptide may be protected from proteolytic degradation with unnatural amino acid analogs at susceptible bonds such as substitution of Tyr by a Tyr analog or substitution of Arg by an Arg analog, and binds to laminin receptors. There are no indicia that the present application enables the full scope in view of a peptide derived from $mEGF_{(33-42)}$ as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how these problems are resolved. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the scope of the claims, the amount of direction or guidance presented, the amount of experimentation necessary and the unpredictability of the art as discussed below.

(1). The scope of the claims

Claims 1-3 encompass a peptide derived from $mEGF_{(33-42)}$ wherein the peptide is modified to protect it from proteolytic degradation, binds to laminin receptors and has substitution of Tyr by a Tyr analog or of Arg by an Arg analog. However, the specification only indicates a peptide obtained from $mEGF_{(33-42)}$ wherein the peptide has certain modification such as substitution of Tyr by Tic-OH or Arg by citrulline or substitution at other positions and the modified peptide is protected from proteolytic degradation and binds to laminin receptors.

(2). The amount of direction or guidance presented and the quantity of experimentation necessary.

The specification indicates a peptide obtained from $mEGF_{(33-42)}$ and having certain modification such as substitution of Tyr by Tic-OH, of Arg by citrulline or modified Cys with Acm is resistant to proteolytic degradation and has antagonist or agonist activity toward laminin

receptors. However, the specification has not identified various peptides which are derived from $mEGF_{(33-42)}$ and have Tyr substituted by any Tyr analog or Arg substituted by any Arg analog nor has demonstrated these peptides are resistant to proteolytic degradation and have antagonist or agonist activity toward laminin receptors. The specification has not shown various Tyr analogs besides Tic-OH or various Arg analogs besides citrulline. Since the Arg analogs or Tyr analogs and the sequences of the peptides derived from $mEGF_{(33-42)}$ are not identified, it is impossible to predict whether the peptides are resistant to proteolytic degradation and their binding activity toward laminin receptors. Therefore, it is necessary to have additional guidance on analogs of Tyr and Arg as well as the sequences of the derived peptides and to carry out further experimentation to assess the antagonist or agonist activities of these peptides.

(3). The unpredictability of the art.

The specification has shown residues at positions 1, 2, 3 and 6 are essential for receptor mediated activities from alanine scanning of the starting peptides ($mEGF_{(33-42)}$), substitution of these individual residues by alanine leads dramatic decrease in receptor affinity (page 23, lines 19-27). The specification also indicates substitution of Tyr at 5 position with Tic-OH converted the antagonist $mEGF_{(33-42)}$ into agonist, and replacement of Arg at 9 position with citrulline increased both receptor binding and inhibition of attachment to laminin substrata but retained antagonist migratory response (page 24, line 35- page 25, line 18). Furthermore, replacement of Asp at position 8 with Ser resulted in a complete loss of biological function, although the analog encompasses the active YIGSR amino acid sequence agonist (page 26, lines 9-22). From the data presented, it is not readily apparent from the specification how the binding activty of the peptide resulting from the modification of the sequence is predicted. Therefore, it is necessary to

perform further experimentation to assess the binding activity of the peptides derived from $mEGF_{(33-42)}$ toward laminin receptor.

Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such peptides in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue because the scope of the claims is broad, the amount of guidance presented is limited (see above), and the working examples do not appear to span the range intended to be covered by the claims. All lead to a requirement for further experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 are indefinite because of the use of the term "derived from", "synthetic equivalent", "consist of at least one modification chosen from the group comprising", "tyrosine analogues" and "arginine analogues". The terms "derived from", "synthetic equivalent", "consist of at least one modification chosen from the group comprising", "tyrosine analogues" and "arginine analogues" render the claim indefinite; it is unclear how different the peptide factor is as compared to parent peptide in the amino acid sequence, whether the synthetic equivalent have the same sequence as the parent peptide or the peptide derived from the parent

peptide, how many modifications are made, whether the modification "consist of" or "comprises" the substitution of tyrosine or arginine by corresponding analogs and what structure the analog has and how different the structure of the analog is as compared to tyrosine or arginine.

6. Claims 2 and 3 are indefinite because of the use of the term "capping the N terminal.....capping thiol groups of cysteines". The term "capping the N terminal.....capping thiol groups of cysteines" renders the claim indefinite; it is unclear what group is used for capping N terminal, C terminal or thiol group of the peptide.

7. Claim 3 is indefinite because of the use of the term "Tic-OH". The term "Tic-OH" renders the claim indefinite; it is unclear what Tic-OH is. A full chemical name should be given at the first occurrence.

Conclusions

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

Christopher S.F. Low

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November 2, 2001

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